National Institute for Health and Care Excellence

Final

Meningitis (bacterial) and meningococcal disease: recognition, diagnosis and management

[F] Evidence review for antibiotics for meningococcal disease

NICE guideline NG240

Evidence review underpinning recommendations 1.7.1 to 1.7.3 in the NICE guideline

March 2024

Final

This evidence review was developed by NICE

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Review question

What antibiotic treatment regimens are effective in treating suspected or confirmed meningococcal disease?

Introduction

Meningococcal disease (meningococcal sepsis with or without an associated meningitis) is a rare but serious infection, which can occur in any age group. Meningococcal disease is a life-threatening infection, which may progress with devastating speed.

The aim of this review is to establish what antibiotic regimens are effective in treating suspected or confirmed meningococcal disease.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with suspected or confirmed meningococcal disease (excluding meningococcal meningitis alone, as this is included in the reviews on bacterial meningitis).

Intervention	Antibiotic agent of interest: • Cefotaxime • Ceftriaxone • Benzylpencillin sodium • Meropenem In cases of severe beta-lactam allergy: Chloramphenicol
Comparison	**Stage 1 (all antibiotic agents of interest):** Comparison: • Cefotaxime or ceftriaxone versus benzylpenicillin sodium alone. • Meropenem versus Cefotaxime or ceftriaxone • Meropenem versus benzylpenicillin sodium alone. **Stage 2 (antibiotic agents identified during stage 1 as most effective/for use where there are contraindications)** Comparisons: • Antibiotic agent A – Dose A vs Antibiotic agent A – Dose B • Antibiotic agent A – Duration of administration A vs Antibiotic agent A – Duration of administration B

Outcome	**Critical** Population: adults, infants and children • All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits [excluding hearing impairment], cognitive deficits*, or behavioural deficits*; measured from discharge up to 1 year after discharge) Population: adults • Functional impairment (measured by any validated scale at any time point) Population: infants and children • Severe developmental delay (defined as score of >2 SD below normal on validated assessment scales, or MDI or PDI <70 on Bayleys assessment scale, or inability to assign a score due to cerebral palsy or severity of cognitive delay; measured at the oldest age reported unless there is substantially more data available at a younger age) **Important** Population: adults, infants and children • Skin, soft tissue or orthopaedic complications requiring surgical intervention (debridement, grafting or amputation) • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant Population: adults • Length of hospitalisation Population: infants and children • Functional impairment (measured by any validated scale at any time point) *For infants and children below school-age, cognitive and behavioural deficits will be assessed at school-age.

MDI: mental development index; PDI: psychomotor development index; SD: standard deviation

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

One randomised controlled trial was included in this review (Tuncer 1988).

The included study is summarised in Table 2.

The study (Tuncer 1988) compared ceftriaxone to benzylpenicillin sodium in babies and children.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summary of the study that was included in this review is presented in Table 2.

Table 2: Summary of included study

Study	Population	Intervention	Comparison	Outcomes	Comments
Tuncer 1988 RCT Turkey	N=42 Babies and children aged 1 month to 12 years with meningococcal disease Age (range): 1 month to 12 years Case-fatality: 7%	Ceftriaxone IV ceftriaxone 80-100 mg/kg once daily for 4 days	Benzylpenicillin sodium IV penicillin G 500,000 units/kg/day in 6 divided doses for 5 days	• All-cause mortality • Skin, soft tissue or orthopaedic complications requiring surgical intervention (debridement, grafting or amputation): Necrotic skin lesions	No clear information on steroid therapy but it states: 12 patients with poor prognostic score received methylprednisolone, volume expanders, dopamine and naloxone Population is indirect due to 67% of population with meningococcal meningitis alone

IV: intravenous; RCT: randomised controlled trial

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Summary of the evidence

This section is a narrative summary of the findings of the review, as presented in the GRADE tables in appendix F. For details of the committee's confidence in the evidence and how this affected recommendations, see The committee's discussion and interpretation of the evidence.

The evidence was assessed as being very low quality due to risk of bias (arising from insufficient information about allocation concealment, blinding, and any deviations from the intended interventions), imprecision (due to low event rates), and the inclusion of an indirect population.

The evidence showed no important difference between ceftriaxone and benzylpenicillin sodium for all-cause mortality in babies and children. There was some evidence for a possibly important difference in necrotic skin lesions with a lower rate associated with ceftriaxone (90% CI 0.01 to 0.67), however, the evidence was very seriously imprecise.

For stage 2 of this review, dose and duration comparisons for antibiotic identified as effective in stage 1 (see summary of the protocol in Table 1), no evidence was identified.

See appendix F for full GRADE tables.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline, but no economic studies were identified which were applicable to this review question.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix J. Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Meningococcal disease is associated with high rates of mortality and morbidity, and antibiotics are the mainstay of treatment for meningococcal disease. Therefore, all-cause mortality and long-term neurological impairment were prioritised as critical outcomes due to the severity of these outcomes. Severe developmental delay was prioritised over functional impairment in children and babies, as it is a more relevant and important outcome for this population. Functional impairment was prioritised as a critical outcome in adults due to the concern about the potential long-term limitations of meningococcal disease on the ability to carry out certain activities of daily life.

In addition to functional impairment (in children and babies), skin, soft tissue or orthopaedic complications requiring surgical intervention, hearing impairment, and serious intervention-related adverse effects were selected as important outcomes in all age groups as these are relatively common after meningococcal disease and may be related to antibiotic therapy. In adults, length of hospitalisation was also chosen as an important outcome because this may be considered as an indicator of treatment effectiveness and was expected to be commonly reported in trials.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology. The evidence for both outcomes was rated as very low quality due to risk of bias (arising from insufficient information about allocation concealment, blinding, and any deviations from the intended interventions), imprecision (due to low event rates), and the inclusion of an indirect population.

No evidence was found that reported long-term neurological impairment, functional impairment, severe developmental delay, hearing impairment, serious intervention-related adverse effects, or length of hospitalisation.

Benefits and harms

The committee considered the evidence comparing ceftriaxone and benzylpenicillin sodium for the treatment of meningococcal disease, that showed no important difference for mortality, and a somewhat lower rate of necrotic skin lesions associated with ceftriaxone. The committee noted that this evidence came from a single small and dated RCT that included an indirect population (the majority of the sample had meningococcal meningitis alone). No other evidence was identified comparing the effectiveness of different antibiotics for the treatment of meningococcal disease. Given the limitations of the evidence, the committee agreed to make recommendations based on their clinical knowledge and experience, and on current practice, and recommended intravenous ceftriaxone for the treatment of suspected or confirmed meningococcal disease. Intravenous ceftriaxone was also recommended as first line treatment for meningococcal disease in the previous NICE guideline (NICE 2010).

The committee were aware that the previous NICE guideline (NICE 2010) recommended 7-day antibiotic treatment for meningococcal disease. The committee acknowledged that practice has changed, and that the previous recommendations were consensus rather than evidence based and pre-dated the widespread use of cephalosporins. The committee discussed that, in some instances, practice has moved to shorter (5-day) courses of antibiotics for the treatment of meningococcal disease without apparent impact on clinical outcomes, although they acknowledged that there is variation in practice. Based on their clinical knowledge and experience, the committee agreed that meningococcus is more sensitive to antibiotics compared with other organisms, particularly cephalosporins such as ceftriaxone. The committee were also aware of evidence from low- and middle-income countries, suggesting that shorter length of treatment may be effective. The committee recommended that people with meningococcal disease should be treated for 5 days with ceftriaxone. The committee agreed that advice from an infection specialist should be sought if the person had not recovered after 5 days.

There was no evidence found on antibiotic use for meningococcal disease in people with an antibiotic allergy, but the committee agreed it was important to make a recommendation for this population. Based on their knowledge and experience, the committee agreed that cephalosporin-induced anaphylaxis is rare, and the risk-benefit balance of ceftriaxone (relative to chloramphenicol as an alternative) is favourable in most patients with non-severe allergy. Therefore, the committee agreed that clinicians should seek information about the nature of the allergy, and ceftriaxone should still be considered if the nature of the allergic reaction they get is not severe, in accordance with the first line treatment recommended above. However, if the allergic reaction is severe, an alternative will be needed. The committee discussed that chloramphenicol is commonly used in the case of severe beta-lactam (penicillin, amoxicillin, or cephalosporin) allergy. Based on clinical knowledge and experience, the committee recommended that advice from an infection specialist (a microbiologist or infectious diseases specialist) should be sought and chloramphenicol should be considered for the antibiotic treatment of meningococcal disease in people with severe antibiotic allergy.

Cost effectiveness and resource use

This review question was not prioritised for economic analysis and therefore the committee made a qualitative assessment of the likely cost-effectiveness of their recommendations. The committee considered that it would be cost-effective to facilitate the option of a shorter course of antibiotics than in previous NICE guidance (NICE 2010) for meningococcal disease as some practice has moved in this direction without any apparent adverse impact on clinical outcomes. However, given the absence of evidence supporting shorter courses in developed countries they did not want to mandate this. The committee believed that by facilitating the option of a shorter course of antibiotics that their recommendation could lead to some small cost savings for the NHS.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.7.1 to 1.7.3.

References – included studies

Effectiveness

Tuncer 1988

Tuncer, A. M., Gür, I., Ertem, U. et al. (1988) Once daily ceftriaxone for meningococcemia and meningococcal meningitis. Pediatric infectious disease journal 7(10): 711-713

Economic

No studies were identified which were applicable to this review question.

Other

NICE 2010

National Institute for Health and Care Excellence (2010). Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management. Available at: https://www.nice.org.uk/guidance/cg102 [Accessed 04/04/2022]

Appendices

Appendix A Review protocols

Review protocol for review question: What antibiotic treatment regimens are effective in treating suspected or confirmed meningococcal disease?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021234215
Review title	Antibiotics for meningococcal disease
Review question	What antibiotic treatment regimens are effective in treating suspected or confirmed meningococcal disease?
Objective	This review aims to find out what is the optimal antibiotic treatment regimen in improving outcomes for people with suspected or confirmed meningococcal disease.
Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: Date limitations: 1980 English language Human studies The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.

Field	Content
Condition or domain being studied	Meningococcal disease
Population	Inclusion: All adults, young people, children and babies (excluding neonates defined as aged 28 days old and younger) with suspected or confirmed meningococcal disease (excluding meningococcal meningitis alone, as this is included in the reviews on bacterial meningitis). Exclusion: People: • with known immunodeficiency. • who have brain tumours, pre-existing hydrocephalus, intracranial shunts, previous neurosurgical procedures, or known cranial or spinal anomalies that increase the risk of bacterial meningitis.
Intervention/Exposure/Test	Antibiotic agent of interest: • Cefotaxime • Ceftriaxone • Benzylpencillin sodium • Meropenem In cases of severe beta-lactam allergy: • Chloramphenicol
Comparator/Reference standard/Confounding factors	Stage 1 (all antibiotic agents of interest): Comparison: • Cefotaxime or ceftriaxone versus benzylpenicillin sodium alone. • Meropenem versus Cefotaxime or ceftriaxone • Meropenem versus benzylpenicillin sodium alone. Stage 2 (antibiotic agents identified during stage 1 as most effective/for use where there are contraindications) Comparisons:

Field	Content
	1. Antibiotic agent A – Dose A vs Antibiotic agent A – Dose B 2. Antibiotic agent A – Duration of administration A vs Antibiotic agent A – Duration of administration B
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • RCTs • If insufficient RCTs: prospective cohort studies • If insufficient prospective cohort studies: retrospective cohort studies Non-randomised studies will be downgraded for risk of bias if they do not adequately adjust for the following covariates, but will not be excluded for this reason: • Co-morbidity • Severity of infection at presentation (including sepsis) • Antibiotics administered pre or post lumbar puncture Exclude: • Conference abstracts
Other exclusion criteria	Cohort studies from low income countries. Studies conducted prior to 1980 as currently used antibiotics were not in common usage prior to this date. Studies published not in English-language
Context	This guidance will fully update the following: Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management (CG102)
Primary outcomes (critical outcomes)	Population: adults • All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits [excluding hearing impairment], cognitive deficits, or behavioural deficits; measured from discharge up to 1 year after discharge) • Functional impairment (measured by any validated scale at any time point)

Field	Content
	Population: infants and children • All-cause mortality (measured up to 1 year after discharge) • Any long-term neurological impairment (defined as any motor deficits, sensory deficits [excluding hearing impairment], cognitive deficits*, or behavioural deficits*; measured from discharge up to 1 year after discharge) • Severe developmental delay (defined as score of >2 SD below normal on validated assessment scales, or MDI or PDI <70 on Bayleys assessment scale, or inability to assign a score due to cerebral palsy or severity of cognitive delay; measured at the oldest age reported unless there is substantially more data available at a younger age) *For infants and children below school-age, cognitive and behavioural deficits will be assessed at school-age.
Secondary outcomes (important outcomes)	Population: adults • Skin, soft tissue or orthopaedic complications requiring surgical intervention (debridement, grafting or amputation) • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant • Length of hospitalisation Population: infants and children • Skin, soft tissue or orthopaedic complications requiring surgical intervention (debridement, grafting or amputation) • Hearing impairment (defined as any level of hearing impairment; measured from discharge up to 1 year after discharge) • Functional impairment (measured by any validated scale at any time point) • Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically

Field	Content
	significant
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will not be undertaken for this question. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • Cochrane ROBINS-I tool for non-randomised (clinical) controlled trials and cohort studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed by visual inspection of the forest plots and consideration of the I2 statistic. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup

Field	Content
	analysis then a random effects model will be used for meta-analysis, or the data will not be pooled if the random effects model does not adequately address heterogeneity. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ **Minimally important differences:** • All-cause mortality: statistical significance • Serious intervention-related adverse effects: statistical significance • Length of hospitalisation: 1 day • Validated scales: Published MIDs where available; if not GRADE default MIDs • All other outcomes: GRADE default MIDs
Analysis of sub-groups	Evidence will be stratified by: Age: • Younger Infants: >28 days to ≤3 months of age • Older infants and children: >3 months to 18* years of age • Adults: ≥18* years of age *There is variation in clinical practice regarding the treatment of 16 to 18 year olds. Therefore, we will be guided by cut-offs used in the evidence when determining if 16 to 18 year olds such be treated as adults or children Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: Age: • Older infants: >3 months to 1 year of age • Children: >1 year to 18 years of age • Young and middle aged adults

Field	Content			
	• Older adults** Meningococcal disease status: • Suspected • Confirmed **There is variation regarding the age at which adults should be considered older adults. Therefore, we will be guided by cut-offs used in the evidence when determining this threshold Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.			
Type and method of review	☒	Intervention		
	☐	Diagnostic		
	☐	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	12/01/2021			
Anticipated completion date	07/12/2023			
Stage of review at time of this submission	Review stage		Started	Completed

Field	Content		
	Preliminary searches	☑	☑
	Piloting of the study selection process	☑	☑
	Formal screening of search results against eligibility criteria	☑	☑
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	Named contact: National Guideline Alliance Named contact e-mail: meningitis&meningococcal@nice.org.uk Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
Review team members	National Guideline Alliance		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline		

Field	Content		
	committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10149.		
Other registration details	None		
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021234215		
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.		
Keywords	Meningococcal disease, antibiotic, anti-bacterial, mortality, impairments		
Details of existing review of same topic by same authors	None		
Current review status	☐	Ongoing	
	☒	Completed but not published	
	☐	Completed and published	
	☐	Completed, published and being updated	
	☐	Discontinued	
Additional information	None		
Details of final publication	www.nice.org.uk		

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MDI: mental development index; MEDLINE: Medical Literature Analysis and Retrieval System Online; MID: minimally important difference; NICE: National Institute for Health and Care Excellence; PDI: psychomotor development index; PRESS: Peer Review of Electronic Search Strategies; RCT: randomised controlled trial; RoB: risk of bias; ROBINS-I: risk of bias in non-randomised studies – of interventions; ROBIS: risk of bias in systematic reviews; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What antibiotic treatment regimens are effective in treating suspected or confirmed meningococcal disease?

Clinical Search

This was a combined search to cover both this review and D1, D2, D3, E1, E2, E3, E4, E5 and E6 on antibiotic regimens for bacterial meningitis (before or in the absence of identifying causative infecting organism and for specific causative organisms) and meningococcal disease.

Database(s): Medline & Embase (Multifile) – OVID interface
Embase Classic+Embase 1947 to 2022 November 09, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to November 09, 2022
Date of last search: 10 November 2022
Multifile database codes: emczd = Embase Classic+Embase; ppez = MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or hemophilus influenzae meningitis/ or listeria meningitis/ or meningococcal meningitis/ or pneumococcal meningitis/ or meningoencephalitis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococ* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) adj3 (septic* or sepsis* or bacter?emi?)).ti,ab.
8	(meningit* or mening?encephalitis*).ti,ab.
9	exp Neisseria meningitidis/ use ppez
10	neisseria meningitidis/ use emczd
11	(Neisseria* mening* or n mening*).ti,ab.
12	or/2,4-11
13	Meningococcal Infections/ use ppez
14	meningococcosis/ or meningococcemia/
15	14 use emczd
16	(meningococc* adj3 (sepsis* or septic* or toxic* or endotoxic* or disease? or infection?)).ti,ab.
17	(meningococcus* or meningococci* or meningococc?emi?).ti,ab.
18	or/13,15-17
19	exp Anti-Bacterial Agents/ or exp Penicillins/ or exp Cephalosporins/ or exp Cefotaxime/ or exp Amoxicillin/ or exp Ampicillin/
20	19 use ppez
21	exp antibiotic agent/ or antibiotic therapy/ or exp penicillin derivative/ or exp cephalosporin derivative/
22	21 use emczd
23	(anti?biotic* or anti?bacterial* or anti?biotherap*).ti,ab.
24	(empiric* adj2 (therap* or treatment*)).ti,ab.
25	(abbocillin or adimicin or alcomicin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin* or aminoglycosid* or amox?cillin* or amoxil* or ampicillin* or ancef or anticepim or apogen or axepim* or ayercillin or azithrom?cin* or benzo?penicillin* or benzyl?penicillin* or bicillin or binotal or biomox or bmy 28142 or bmy?28142 or bristagen or bristamox or carbapenem* or cedax or ceftazidim* or cefatriaxon* or cefepim* or cefixim* or cefizox or cefobid* or cefotan or cefotaxim* or ceftaroline* or ceftin or ceftolozane* or ceftriaxon* or ceftriazon* or cefuroxim* or cefzil or cepazin* or cephalosporin* or cephotaxim* or cephuroxim* or cepim?x or chloramphenicol* or ciprofloxacin* or claforan or clamoxyl or clarithromycin* or clindamycin* or colistin* or compocillin or cosmopen or cotrimoxazol* or co trimoxazol* or crysticillin or delafloxacin* or deripen or dexamethasone or diatracin or doktacillin or duricef or elobact or erythromycin* or flucloxacillin* or fluoroquinolon* or fosfomycin* or gelacillin or gentam?cin* or gent?mycin* or gentamyl* or gentamytrex or gentaplus or gentarad or gentaso* or gentasporin or gentatrim or gent?cin* or gent?cyn* or geocillin* or geomycin* or glycopeptid* or guicitrin* or hexam?cin* or hiconcil or histocillin or ibiamox or imacillin or jenamicin or kefurox or kefzol or klaforan or lendacin or levofloxacin* or linezolid* or longacef or longaceph or lyphocin or macrolide* or mandol or maxcef or maxipim* or mefoxin or megacillin or meropen* or miram?cin* or monocid or moxacin or moxifloxacin* or ofloxacin* or oftagen* or omnipen or optigen* or pefloxacin* or penbritin* or penbrock or penicillin? or penicline or pentids or pentrex or pentrexl or pentrexyl or permapen or pfizerpen or polycillin or polymox or

#	Searches
	polymyxin*or primafen or principen or quinolon* or refobacin* or ribom?cin* or rifampicin or rifampin* or rocefalin or rocefin or rocephin* or roscillin or rufloxacin* or sagestam* or spectrobid or sulm?cin* or supen or tazobactam* or terram?cin* or tetracycline* or tobramycin* or totacillin or totapen or trimox or u?gencin* or ukapen or ultrabion or vamysin or vancam* or vanccostacin or vancin or vancom* or vancomycin* or vankom* or velosef or vetramox* or viccillin or voncon* or wycillin or zimox or zinacef or zin?at).mp.
26	or/20,22-25
27	(12 or 18) and 26
28	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
29	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
30	meta-analysis/
31	meta-analysis as topic/
32	systematic review/
33	meta-analysis/
34	(meta analy* or metanaly* or metaanaly*).ti,ab.
35	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
36	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
37	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
38	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
39	(search* adj4 literature).ab.
40	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
41	cochrane.jw.
42	((pool* or combined) adj2 (data or trials or studies or results)).ab.
43	letter/
44	editorial/
45	news/
46	exp historical article/
47	Anecdotes as Topic/
48	comment/
49	case report/
50	(letter or comment*).ti.
51	43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52	randomized controlled trial/ or random*.ti,ab.
53	51 not 52
54	animals/ not humans/
55	exp Animals, Laboratory/
56	exp Animal Experimentation/
57	exp Models, Animal/
58	exp Rodentia/
59	(rat or rats or mouse or mice).ti.
60	53 or 54 or 55 or 56 or 57 or 58 or 59
61	letter.pt. or letter/
62	note.pt.
63	editorial.pt.
64	case report/ or case study/
65	(letter or comment*).ti.
66	61 or 62 or 63 or 64 or 65
67	randomized controlled trial/ or random*.ti,ab.
68	66 not 67
69	animal/ not human/
70	nonhuman/
71	exp Animal Experiment/
72	exp Experimental Animal/
73	animal model/
74	exp Rodent/
75	(rat or rats or mouse or mice).ti.
76	68 or 69 or 70 or 71 or 72 or 73 or 74 or 75
77	60 use ppez
78	76 use emczd
79	77 or 78
80	28 use ppez
81	29 use emczd
82	80 or 81
83	(or/30-31,34,36-41) use ppez
84	(or/32-35,37-42) use emczd
85	83 or 84
86	27 not 79
87	limit 86 to English language

#	Searches
88	limit 87 to yr="1980 -Current"
89	limit 88 to (conference abstract or conference paper or conference review or conference proceeding) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
90	89 use emczd
91	88 not 90
92	82 or 85
93	91 and 92 [SR/RCT data]
94	91 not 93 [Non-RCT data]

Database(s): Cochrane Library – Wiley interface
Cochrane Database of Systematic Reviews, Issue 11 of 12, November 2022, **Cochrane Central Register of Controlled Trials**, Issue 11 of 12, November 2022
Date of last search: 10 November 2022

#	Searches
#1	MeSH descriptor: [Meningitis] this term only
#2	MeSH descriptor: [Meningitis, Bacterial] this term only
#3	MeSH descriptor: [Meningitis, Escherichia coli] this term only
#4	MeSH descriptor: [Meningitis, Haemophilus] this term only
#5	MeSH descriptor: [Meningitis, Listeria] this term only
#6	MeSH descriptor: [Meningitis, Meningococcal] this term only
#7	MeSH descriptor: [Meningitis, Pneumococcal] this term only
#8	MeSH descriptor: [Meningoencephalitis] this term only
#9	MeSH descriptor: [Neisseria meningitidis] explode all trees
#10	((bacter* or infect*) near/3 (mening* or leptomening* or subarachnoid space*)):ti,ab,kw
#11	(("e coli" or "escherichia coli" or haemophilus or hemophilus or hib or (h next influenz*) or listeria* or pneumococc* or (gram next negativ* next bacill*) or streptococ* or GBS or (s next pneumon*)) near/3 (septic* or sepsis* or bacteraemi* or bacteremi* or infect*)):ti,ab,kw
#12	(meningit* or mening?encephalitis* or (mening* next encephalitis*)).:ti,ab,kw
#13	((neisseria* next mening*) or (n next mening*)):ti,ab,kw
#14	MeSH descriptor: [Meningococcal Infections] this term only
#15	meningococc*:ti,ab,kw
#16	{or #1-#15}
#17	MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#18	((antibiotic* or antibacterial* or antibiotherap* or "anti biotic*" or "anti bacterial*" or "anti biotherap*")):ti,ab,kw
#19	((empiric* near/2 (therap* or treatment*))):ti,ab,kw
#20	((abbocillin or adimicin or alcomicin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin* or aminoglycosid* or amox?cillin* or amoxil* or ampicillin* or ancef or anticepim or apogen or axepim* or ayercillin or azithrom?cin* or benzo?penicillin* or benzyl?penicillin* or bicillin or binotal or biomox or bmy 28142 or bmy?28142 or bristagen or bristamox or carbapenem* or cedax or ceftazidim* or cefatriaxon* or cefepim* or cefixim* or cefizox or cefobid* or cefotan or cefotaxim* or ceftaroline* or ceftin or ceftolozane* or ceftriaxon* or ceftriazon* or cefuroxim* or cefzil or cepazin* or cephalosporin* or cephotaxim* or cephuroxim* or cepim?x or chloramphenicol* or ciprofloxacin* or claforan or clamoxyl or clarithromycin* or clindamycin* or colistin* or compocillin or cosmopen or cotrimoxazol* or co trimoxazol* or crysticillin or delafloxacin* or deripen or dexamethasone or diatracin or doktacillin or duricef or elobact or erythromycin* or flucloxacillin* or fluoroquinolon* or fosfomycin* or gelacillin or gentam?cin* or gent?mycin* or gentamyl* or gentamytrex or gentaplus or gentarad or gentaso* or gentasporin or gentatrim or gent?cin* or gent?cyn* or geocillin* or geomycin* or glycopeptid* or guicitrin* or hexam?cin* or hiconcil or histocillin or ibiamox or imacillin or jenamicin or kefurox or kefzol or klaforan or lendacin or levofloxacin* or linezolid* or longacef or longaceph or lyphocin or macrolide* or mandol or maxcef or maxipim* or mefoxin or megacillin or meropen* or miram?cin* or monocid or moxacin or moxifloxacin* or ofloxacin* or oftagen* or omnipen or optigen* or pefloxacin* or penbritin* or penbrock or penicillin? or penicline or pentids or pentrex or pentrexl or pentrexyl or permapen or pfizerpen or polycillin or polymox or polymyxin*or primafen or principen or quinolon* or refobacin* or ribom?cin* or rifampicin or rifampin* or rocefalin or rocefin or rocephin* or roscillin or rufloxacin* or sagestam* or spectrobid or sulm?cin* or supen or tazobactam* or terram?cin* or tetracycline* or tobramycin* or totacillin or totapen or trimox or u?gencin* or ukapen or ultrabion or vamysin or vancam* or vanccostacin or vancin or vancom* or vancomycin* or vankom* or velosef or vetramox* or viccillin or voncon* or wycillin or zimox or zinacef or zin?at)):ti,ab,kw
#21	{or #17-#20}
#22	#16 and #21
#23	"conference":pt or (clinicaltrials or trialsearch):so
#24	#22 not #23

Database(s): Database of Abstracts of Reviews of Effects (DARE); HTA Database – CRD interface
Date of last search: 12 February 2021

#	Searches
1	MeSH DESCRIPTOR meningitis IN DARE,HTA
2	MeSH DESCRIPTOR meningitis, bacterial IN DARE,HTA
3	MeSH DESCRIPTOR Meningitis, Escherichia coli IN DARE,HTA
4	MeSH DESCRIPTOR Meningitis, Haemophilus IN DARE,HTA

#	Searches
5	MeSH DESCRIPTOR Meningitis, Listeria IN DARE,HTA
6	MeSH DESCRIPTOR Meningitis, Meningococcal IN DARE,HTA
7	MeSH DESCRIPTOR Meningitis, Pneumococcal IN DARE,HTA
8	MeSH DESCRIPTOR Meningoencephalitis IN DARE,HTA
9	MeSH DESCRIPTOR Meningococcal infections IN DARE,HTA
10	(((((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or "subarachnoid space*"))))) IN DARE, HTA
11	(meningit*) IN DARE, HTA
12	((((meningencephalitis* or meningoencephalitis*)))) IN DARE, HTA
13	((((meningococc* NEAR3 (sepsis* or septic* or toxic* or endotoxic* or disease or diseases or infection or infections))))) IN DARE, HTA
14	((((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*)))) IN DARE, HTA
15	((Neisseria* NEAR1 mening*)) IN DARE, HTA
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17	MeSH DESCRIPTOR Anti-Bacterial Agents EXPLODE ALL TREES IN DARE,HTA
18	MeSH DESCRIPTOR Penicillins EXPLODE ALL TREES IN DARE,HTA
19	MeSH DESCRIPTOR Cephalosporins EXPLODE ALL TREES IN DARE,HTA
20	MeSH DESCRIPTOR Cefotaxime EXPLODE ALL TREES IN DARE,HTA
21	MeSH DESCRIPTOR Amoxicillin EXPLODE ALL TREES IN DARE,HTA
22	MeSH DESCRIPTOR Ampicillin EXPLODE ALL TREES IN DARE,HTA
23	(((antibiotic* or antibacterial* or antibiotherap* or anti-biotic* or anti-bacterial* or anti-biotherap* or "anti biotic*" or "anti bacterial*" or "anti biotherap*"))) IN DARE, HTA
24	(((empiric* NEAR2 (therap* or treatment*)))) IN DARE, HTA
25	(((abbbocillin or adimicin or alcomicin or alpen or amblosin or amcill or amfipen or aminobenzylpenicillin or amox?cillin or amoxil* or ampicillin or ancef or anticepim or apogen or axepim* or ayercillin or benzo?penicillin* or benzyl?penicillin* or bicillin or binotal or biomox or bmy 28142 or bmy-28142 or bmy28142 or bristagen or bristamox or cedax or cefatriaxon* or cefepim* or cefixim* or cefizox or cefobid* or cefotan or cefotaxim* or ceftin or ceftriaxon* or ceftriazon* or cefuroxim* or cefzil or cepazin* or cephotaxim* or cephuroxim* or cepim?x or chloramphenicol or claforan or clamoxyl or compocillin or cosmopen or cotrimoxazol* or co trimoxazol* or co-trimoxazol or crysticillin or deripen or dexamethasone or diatracin or doktacillin or duricef or elobact or gelacillin or gentam?cin* or gent?mycin* or gentamyl* or gentamytrex or gentaplus or gentarad or gentaso* or gentasporin or gentatrim or gent?cin* or gent?cyn* or geocillin* or geomycin* or guicitrin* or hexam?cin* or hiconcil or histocillin or ibiamox or imacillin or jenamicin or kefurox or kefzol or klaforan or lendacin or longacef or longaceph or lyphocin or mandol or maxcef or maxipim* or mefoxin or megacillin or meropen* or miram?cin* or monocid or moxacin or oftagen* or omnipen or optigen* or penbritin* or penbrock or penicillin? or penicline or pentids or pentrex or pentrexl or pentrexyl or permapen or pfizerpen or polycillin or polymox or primafen or principen or refobacin* or ribom?cin* or rifampicin or rocefalin or rocefin or rocephin* or roscillin or sagestam* or spectrobid or sulm?cin* or supen or terram?cin* or totacillin or totapen or trimox or u?gencin* or ukapen or ultrabion or vamysin or vancam* or vanccostacin or vancin or vancom* or vancomycin or vankom* or velosef or vetramox* or viccillin or voncon* or wycillin or zimox or zinacef or zin?at))) IN DARE, HTA
26	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
27	#16 AND #26

Economic Search

One global search was conducted for economic evidence across the guideline.

Database(s): NHS Economic Evaluation Database (NHS EED), HTA Database – CRD interface

Date of last search: 11 March 2021

#	Searches
1	MeSH DESCRIPTOR meningitis IN NHSEED,HTA
2	MeSH DESCRIPTOR Meningitis, Bacterial IN NHSEED,HTA
3	MeSH DESCRIPTOR Meningitis, Escherichia coli IN NHSEED,HTA
4	MeSH DESCRIPTOR Meningitis, Haemophilus EXPLODE ALL TREES IN NHSEED,HTA
5	MeSH DESCRIPTOR Meningitis, Listeria IN NHSEED,HTA
6	MeSH DESCRIPTOR Meningitis, Meningococcal IN NHSEED,HTA
7	MeSH DESCRIPTOR Meningitis, Pneumococcal IN NHSEED,HTA
8	MeSH DESCRIPTOR Meningoencephalitis IN NHSEED,HTA
9	(((bacter* or infect*) NEAR3 (meningit* or meninges* or leptomeninges* or subarachnoid space*))) IN NHSEED, HTA
10	((meningit* NEAR3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?))) IN NHSEED, HTA
11	(((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) NEAR3 (septic* or sepsis* or bacter?emi?))) IN NHSEED, HTA
12	((meningencephalitis* or meningoencephalitis* or meningit*)) IN NHSEED, HTA
13	MeSH DESCRIPTOR Meningococcal Infections IN NHSEED,HTA

#	Searches
14	MeSH DESCRIPTOR Neisseria meningitidis EXPLODE ALL TREES IN NHSEED,HTA
15	((meningococc* NEAR3 (sepsis* or septic* or toxic* or endotoxic* or disease* or infection*))) IN NHSEED, HTA
16	((meningococcus* or meningococci* or meningococcaemia* or meningococcemia*)) IN NHSEED, HTA
17	((Neisseria* NEXT mening*)) IN NHSEED, HTA
18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

Database(s): Medline & Embase (Multifile) – OVID interface
Embase Classic+Embase 1947 to 2022 November 09, **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to November 09, 2022
Date of last search: 10 November 2022
Multifile database codes: emczd = Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	Searches
1	Meningitis/ or Meningitis, Bacterial/ or Meningitis, Escherichia Coli/ or Meningitis, Haemophilus/ or Meningitis, Listeria/ or Meningitis, Meningococcal/ or Meningitis, Pneumococcal/ or Meningoencephalitis/
2	1 use ppez
3	meningitis/ or bacterial meningitis/ or haemophilus meningitis/ or listeria meningitis/ or pneumococcal meningitis/ or meningoencephalitis/
4	3 use emczd
5	((bacter* or infect*) adj3 (meningit* or meninges* or leptomeninges* or subarachnoid space?)).ti,ab.
6	(meningit* adj3 (e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon* or septic* or sepsis* or bacter?emi?)).ti,ab.
7	((e coli or escherichia coli or h?emophilus or hib or h?emophilus influenz* or h influenz* or listeria* or meningococc* or pneumococc* or gram-negativ* bacill* or gram negativ* bacill* or streptococc* or group B streptococc* or GBS or streptococcus pneumon* or s pneumon*) adj3 (septic* or sepsis* or bacter?emi?)).ti,ab.
8	(mening?encephalitis* or meningit*).ti,ab.
9	or/2,4-8
10	Meningococcal Infections/ or exp Neisseria meningitidis/
11	10 use ppez
12	Meningococcosis/ or Meningococcemia/ or Neisseria Meningitidis/
13	12 use emczd
14	(meningococc* adj3 (sepsis* or septic* or toxic* or endotoxic* or disease? or infection?)).ti,ab.
15	(meningococcus* or meningococci* or meningococc?emi?).ti,ab.
16	(Neisseria* mening* or n mening*).ti,ab.
17	or/11,13-16
18	Economics/ use ppez
19	Value of life/ use ppez
20	exp "Costs and Cost Analysis"/ use ppez
21	exp Economics, Hospital/ use ppez
22	exp Economics, Medical/ use ppez
23	Economics, Nursing/ use ppez
24	Economics, Pharmaceutical/ use ppez
25	exp "Fees and Charges"/ use ppez
26	exp Budgets/ use ppez
27	health economics/ use emczd
28	exp economic evaluation/ use emczd
29	exp health care cost/ use emczd
30	exp fee/ use emczd
31	budget/ use emczd
32	funding/ use emczd
33	budget*.ti,ab.
34	cost*.ti.
35	(economic* or pharmaco?economic*).ti.
36	(price* or pricing*).ti,ab.
37	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
38	(financ* or fee or fees).ti,ab.
39	(value adj2 (money or monetary)).ti,ab.
40	or/18-39
41	Quality-Adjusted Life Years/ use ppez
42	Sickness Impact Profile/
43	quality adjusted life year/ use emczd
44	"quality of life index"/ use emczd
45	(quality adjusted or quality adjusted life year*).tw.
46	(qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw.
47	(illness state* or health state*).tw.
48	(hui or hui2 or hui3).tw.

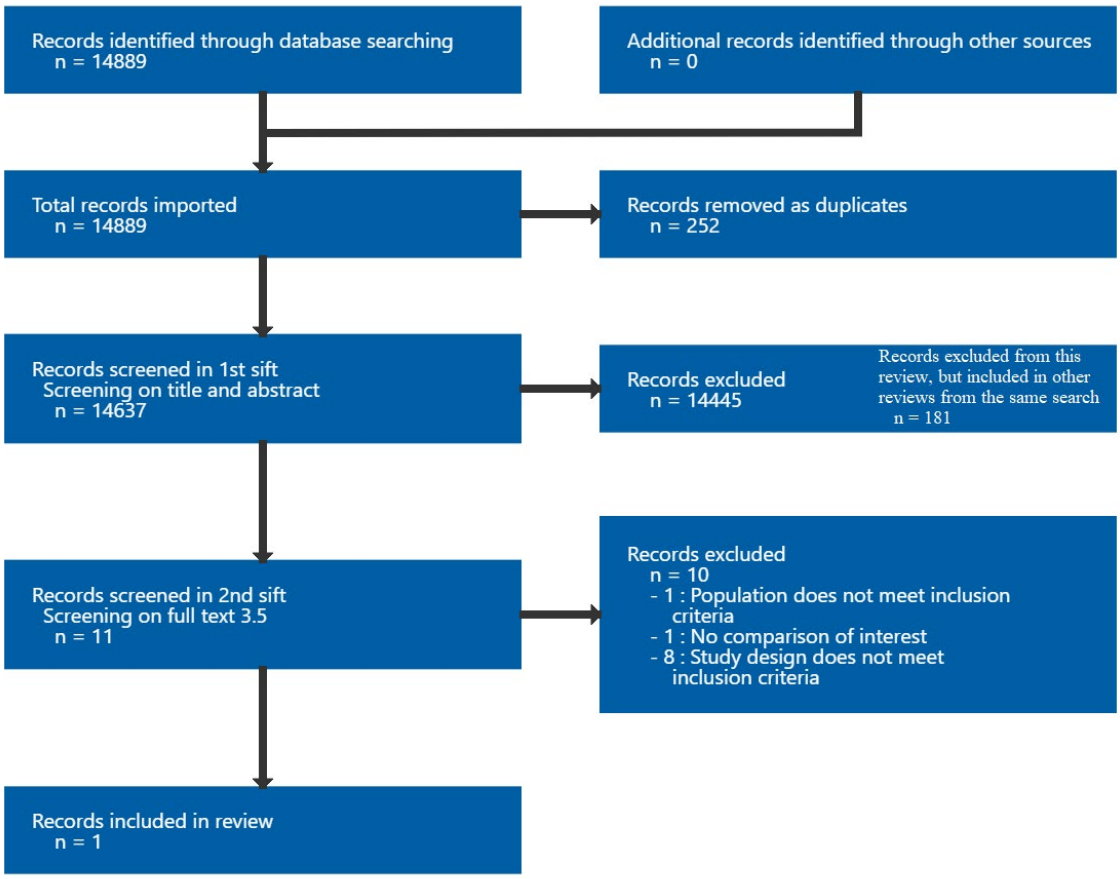
#	Searches
49	(multiattibute* or multi attribute*).tw.
50	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
51	utilities.tw.
52	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw.
53	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw.
54	(sf36 or sf 36 or sf thirty six or sf thirtysix).tw.
55	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
56	Quality of Life/ and ((quality of life or qol) adj (score*1 or measure*1)).tw.
57	Quality of Life/ and ec.fs.
58	Quality of Life/ and (health adj3 status).tw.
59	(quality of life or qol).tw. and Cost-Benefit Analysis/ use ppez
60	(quality of life or qol).tw. and cost benefit analysis/ use emczd
61	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improv* or declin* or reduc* or high* or low* or effect or effects or worse or score or scores or change*1 or impact*1 or impacted or deteriorat*)).ab.
62	Cost-Benefit Analysis/ use ppez and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
63	cost benefit analysis/ use emczd and cost-effectiveness ratio*.tw. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.
64	*quality of life/ and (quality of life or qol).ti.
65	quality of life/ and ((quality of life or qol) adj3 (improv* or chang*)).tw.
66	quality of life/ and health-related quality of life.tw.
67	Models, Economic/ use ppez
68	economic model/ use emczd
69	care-related quality of life.tw,kw.
70	((capability$ or capability-based$) adj (measure$ or index or instrument$)).tw,kw.
71	social care outcome$.tw,kw.
72	(social care and (utility or utilities)).tw,kw.
73	or/41-72
74	(9 or 17) and 40
75	(9 or 17) and 73
76	letter/
77	editorial/
78	news/
79	exp historical article/
80	Anecdotes as Topic/
81	comment/
82	case report/
83	(letter or comment*).ti.
84	76 or 77 or 78 or 79 or 80 or 81 or 82 or 83
85	randomized controlled trial/ or random*.ti,ab.
86	84 not 85
87	animals/ not humans/
88	exp Animals, Laboratory/
89	exp Animal Experimentation/
90	exp Models, Animal/
91	exp Rodentia/
92	(rat or rats or mouse or mice).ti.
93	86 or 87 or 88 or 89 or 90 or 91 or 92
94	letter.pt. or letter/
95	note.pt.
96	editorial.pt.
97	case report/ or case study/
98	(letter or comment*).ti.
99	94 or 95 or 96 or 97 or 98
100	randomized controlled trial/ or random*.ti,ab.
101	99 not 100
102	animal/ not human/
103	nonhuman/
104	exp Animal Experiment/
105	exp Experimental Animal/
106	animal model/
107	exp Rodent/
108	(rat or rats or mouse or mice).ti.
109	101 or 102 or 103 or 104 or 105 or 106 or 107 or 108
110	93 use ppez
111	109 use emczd
112	110 or 111
113	74 not 112

#	Searches
114	limit 113 to English language
115	75 not 112
116	limit 115 to English language
117	114 or 116

Appendix C Effectiveness evidence study selection

Study selection for: What antibiotic treatment regimens are effective in treating suspected or confirmed meningococcal disease?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What antibiotic treatment regimens are effective in treating suspected or confirmed meningococcal disease?

Table 4: Evidence tables – effectiveness evidence

Tuncer, 1988

Bibliographic Reference Tuncer, A. M.; Gür, I.; Ertem, U.; Ece, A.; Türkmen, S.; Deniz, B.; Gürman, I.; Tuncer, S.; Once daily ceftriaxone for meningococcemia and meningococcal meningitis; Pediatric infectious disease journal; 1988; vol. 7 (no. 10); 711-713

Study details

Country/ies where study was carried out	Turkey
Study type	Randomised controlled trial (RCT)
Study dates	January 1987 – June 1987
Inclusion criteria	Babies and children aged 1 month to 12 years with meningococcal disease. Meningococcal disease defined as positive CSF or blood culture for N. meningitidis, or identification of Gram-negative diplococci in CSF, or meningitis with or without purpura
Exclusion criteria	Not reported
Patient characteristics	N=42 Age (range): 1 month to 12 years Sex: male: 23 (55%); female: 19 (45%) Etiology: Neisseria meningitidis group B: 2 (5%); Neisseria meningitidis group C: 40 (95%)

Intervention(s)/control	Ceftriaxone: Intravenous ceftriaxone single daily dose of 80-100 mg/kg for 4 days Benzylpenicillin sodium: Intravenous penicillin G 500,000 units/kg/day in 6 divided doses for 5 days
Duration of follow-up	Babies and children were assessed during hospitalisation.
Sources of funding	Not reported
Sample size	N=42
Other information	No clear information on steroid therapy but it states: Twelve patients with poor prognostic score received methylprednisolone, volume expanders, dopamine and naloxone. Population is indirect as it included participants with meningococcal meningitis alone (67%).

CSF: cerebrospinal fluid; RCT: randomised controlled trial

Outcomes

Ceftriaxone versus benzylpenicillin sodium: All-cause mortality and skin, soft tissue or orthopaedic complications requiring surgical intervention (debridement, grafting or amputation)

Outcome	Ceftriaxone, N = 20	Benzylpenicillin sodium, N = 22
All-cause mortality (during hospitalisation) No of events	n = 1	n = 2
Skin, soft tissue or orthopaedic complications requiring surgical intervention (debridement, grafting or amputation): Necrotic skin lesions (during hospitalisation) No of events	n = 0	n = 8

CSF: cerebrospinal fluid; RCT: randomised controlled trial

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information about allocation concealment was provided. No significant differences between groups at baseline.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(No information on blinding. No information on whether deviations arose because of the trial context. Appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Outcome data was available for all participants.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Measurement did not differ between groups. Knowledge of the assigned intervention could not influence the outcome.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that all eligible reported results for the outcome correspond to all intended outcome measurements and analyses.)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(The study is judged to raise some concerns in at least one domain.)*
Overall bias and Directness	Overall Directness	High (*Population is indirect due to participants with meningococcal meningitis alone [67%]*)
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Appendix E Forest plots

Forest plots for review question: What antibiotic treatment regimens are effective in treating suspected or confirmed meningococcal disease?

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F GRADE tables

GRADE tables for review question: What antibiotic treatment regimens are effective in treating suspected or confirmed meningococcal disease?

Table 5: Evidence profile for comparison: ceftriaxone versus benzylpenicillin sodium

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone	Benzylpenicillin sodium	Relative (95% CI)	Absolute		
All-cause mortality: babies and children (during hospitalisation)												
1 (Tuncer 1988)	randomised trials	serious[1]	no serious inconsistency	very serious[2]	very serious[3]	none	1/20 (5%)	2/22 (9.1%)	RR 0.55 (0.05 to 5.61)	41 fewer per 1000 (from 86 fewer to 419 more)	VERY LOW	CRITICAL
Skin, soft tissue or orthopaedic complications requiring surgical intervention (debridement, grafting or amputation) - Necrotic skin lesions: babies and children (during hospitalisation)												
1 (Tuncer 1988)	randomised trials	serious[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	0/20 (0%)	8/22 (36.4%)	RR 0.06 (0.004 to 1.05)	342 fewer per 1000 (from 362 fewer to 18 more)	VERY LOW	IMPORTANT

CI: confidence interval; RR: risk ratio

[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[2] Population is indirect due to participants with meningococcal meningitis alone (67%)

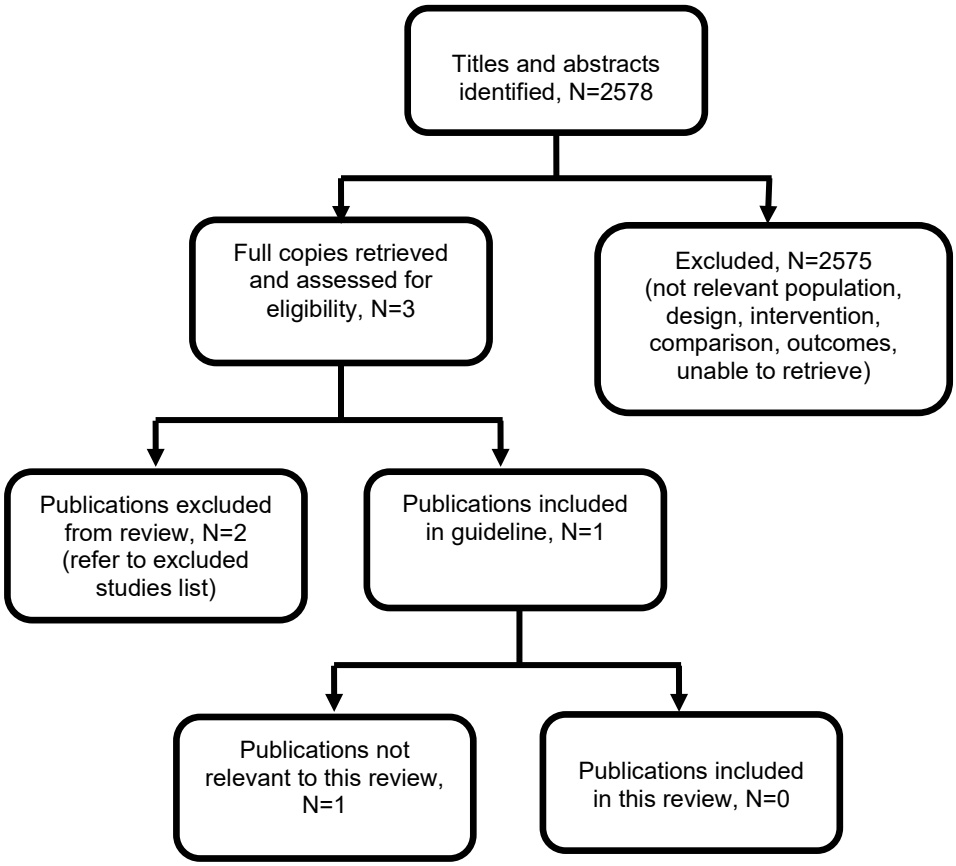
[3] <150 events

Appendix G Economic evidence study selection

Study selection for: What antibiotic treatment regimens are effective in treating suspected or confirmed meningococcal disease?

A global economic search was undertaken for the whole guideline, but no economic evidence was identified which was applicable to this review question (see Figure 2).

Figure 2: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What antibiotic treatment regimens are effective in treating suspected or confirmed meningococcal disease?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What antibiotic treatment regimens are effective in treating suspected or confirmed meningococcal disease?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What antibiotic treatment regimens are effective in treating suspected or confirmed meningococcal disease?

Excluded effectiveness studies

The excluded studies table only lists the studies that were considered and then excluded at the full-text stage for this review (N=10) and not studies (N=181) that were considered and then excluded from the search at the full-text stage as per the PRISMA diagram in Appendix C for the other review questions in the same search.

Table 6: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Baumer, J. H. (2009) Guideline review: Management of invasive meningococcal disease, SIGN. Archives of Disease in Childhood: Education and Practice Edition 94(2): 46-49	- Study design does not meet inclusion criteria
Briggs, S., Ellis-Pegler, R., Roberts, S. et al. (2004) Short course intravenous benzylpenicillin treatment of adults with meningococcal disease. Internal medicine journal 34(7): 383-7	- Study design does not meet inclusion criteria
Broom, Matthew, Best, Emma, Heffernan, Helen et al. (2022) Outcomes of adults with invasive meningococcal disease with reduced penicillin susceptibility in Auckland 2004-2017. Infection	- Study design does not meet inclusion criteria
Cabellos, C., Pelegrin, I., Benavent, E. et al. (2017) Invasive meningococcal disease: Impact of short course therapy. A DOOR/RADAR study. Journal of Infection 75(5): 420-425	- No comparison of interest
Choonara, I. and Bullock, D. (2001) Treatment of meningococcal disease, is longer better?. Paediatric and Perinatal Drug Therapy 4(4): 168	- Study design does not meet inclusion criteria
Ellis-Pegler, Rod, Galler, Lesley, Roberts, Sally et al. (2003) Three days of intravenous benzyl penicillin treatment of meningococcal disease in adults. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 37(5): 658-62	- Study design does not meet inclusion criteria
Fitzgerald, Deirdre and Waterer, Grant W. (2019) Invasive Pneumococcal and Meningococcal Disease. Infectious disease clinics of North America 33(4): 1125-1141	- Study design does not meet inclusion criteria
Halstensen, A.; Vollset, S. E.; Haneberg, B. (1987) Antimicrobial therapy and case fatality in meningococcal disease. Scandinavian Journal of Infectious Diseases 19(4): 403-407	- Study design does not meet inclusion criteria

Study	Code [Reason]
Kumar, A., Safdar, N., Kethireddy, S. et al. (2010) A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: a meta-analytic/meta-regression study. Critical Care Medicine 38(8): 1651-1664	- Population does not meet inclusion criteria
Sarfatti, A. and Nadel, S. (2019) Management of meningococcal disease. Paediatrics and Child Health (United Kingdom) 29(5): 197-204	- Study design does not meet inclusion criteria

Excluded economic studies

Study	Code [Reason]
Duff, S., Hasbun, R., Balada-Llasat, J. M., Zimmer, L., Bozzette, S. A., Ginocchio, C. C., Economic analysis of rapid multiplex polymerase chain reaction testing for meningitis/encephalitis in adult patients, Infection, 20, 20, 2019	Excluded as rated not applicable. US resource use and costs and judged unlikely to be applicable to current UK NHS context.
Duff, S., Hasbun, R., Ginocchio, C. C., Balada-Llasat, J. M., Zimmer, L., Bozzette, S. A., Economic analysis of rapid multiplex polymerase chain reaction testing for meningitis/encephalitis in pediatric patients, Future Microbiology, 13, 617-629, 2018	Excluded as rated not applicable. US resource use and costs and judged unlikely to be applicable to current UK NHS context.

Appendix K Research recommendations – full details

Research recommendations for review question: What antibiotic treatment regimens are effective in treating suspected or confirmed meningococcal disease?

No research recommendation was made for this review.